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*N*1,*N*3-Diacyl-3,4-dihydropyrimidin-2(1*H*)-ones: neutral acyl group transfer reagents

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ABSTRACT

Readily available *N*1,*N*3-diacyl-3,4-dihydropyrimidin-2(1*H*)-ones efficiently acylate ammonia, primary and secondary amines to furnish primary, secondary and tertiary amides in good to excellent yields. The wide applicability of the procedure is demonstrated by running the reactions in a neutral medium, easy isolation of products, recycling of the innocuous by-product and chemoselectivity of the transformation.

1. Introduction

Amine protection[1] through an acylation reaction is one of the most fundamental operations encountered during a diverse range of multi-step organic synthesis sequences, where blocking of both basic as well as nucleophilic group is necessitated. This objective in routine is achieved by the use of an acid or base catalyzed direct acylations using acids or activated derivatives of acids such as acyl halides[2] and anhydrides and even esters under rather harsh conditions. Alternatively acyl transfer reagents have also been employed in a number of instances.[3] Quite useful chemoselective acylation reactions of amine in aqueous media have also been demonstrated in the ambit of 'green' chemistry.[4] Each method has its advantages (chemoselectivity, higher yields, formation of non-toxic by-products, mild reaction conditions), and disadvantages (expensive reagents, non-suitability for large scale preparations, exothermic nature, formation of imide by-products in case of anhydrides, requirement of strongly basic catalysts and/or high pressure). Thus acyl transfers using a readily accessible agent, capable of performing chemoselective acylations under neutral conditions and forms innocuous by-products are highly desirable and we now report a simple, mild and general procedure for the preparation of primary, secondary and tertiary amides. 3,4-Dihydropyrimidinones are available in kilogram quantities through three-component Biginelli condensation reaction[5] and can be conveniently converted through one-pot acylation reaction to *N*1,*N*3-diacyl-3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) and subsequently treated with ammonia, primary or secondary amines to obtain amides. We reason that owing to the inbuilt difference in basicity of N1 (enaminoester nitrogen) and comparatively electron rich N3, the acyl group at N1 is expected to be more electrophilic and prone to acyl transfer to nucleophilic sites. Herein we demonstrate the feasibility of using *N*1,*N*3-diacylated DHPMs as acyl transfer agents.

2. Results and discussion

3,4-Dihydropyrimidin-2(1*H*)-ones **1**[5] readily available from three-component Biginelli condensation and a number of variants was previously converted into *N*1,*N*3-diacyl-3,4-dihydropyrimidin-2(1*H*)-ones **2** through reaction with appropriate acid chlorides albeit in lower yields.[6] We now find that derivatives of **2** are produced in up to 78% yield by treatment of appropriate **1** with an anhydride or acid chloride when the reaction is performed at relatively higher temperature (Scheme 1). Thus reaction of **1** with propionic anhydride, acetic anhydride, butyric anhydride, benzoyl chloride or *p*-methoxy benzoyl chloride (vide experimental) furnished appropriate *N*1,*N*3-diacylated 3,4-dihydropyrimidin-2(1*H*)-ones **2a**–**e** in 55, 60, 78, 67 and 64% yields, respectively. It was also found that different acyl substituents could be appended on **2** in high yield, without altering the reaction profile, making it a generalized methodology for the synthesis of a number of derivatives of

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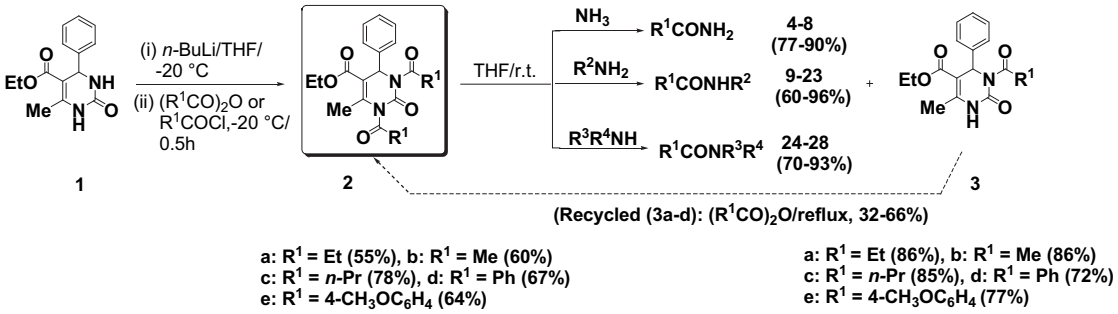

Scheme 1. Acylation of 3,4-dihydropyrimidin-2(1*H*)-ones and preparation of amides.

2. Structures of these reagents were unambiguously supported by ^{1}H, ^{13}C NMR spectra and microanalysis.

Treatment of *N*1,*N*3-diacylated 3,4-dihydropyrimidin-2(1*H*)-ones **2a**–**e** with THF saturated with ammonia gas at room temperature for around 1 h gave corresponding amides, which after column chromatographic separation were recrystallized from dichloromethane and hexane mixtures to afford pure primary amides **4**–**8** (Scheme 1). The yields and melting points as well as literature melting points for the primary amides **4**–**8** are summarized in Table 1. The melting points and the spectral data are in accord with literature data. The *N*3-acyl 3,4-dihydropyrimidin-2(1*H*)-ones **3a**–**e** were isolated quantitatively and recycled to obtain corresponding **2a**–**d** (Scheme 1).

Table 1
Preparation (THF/rt) of primary amides **4**–**8** (R^1CONH_2) from ammonia

Primary amides	R^1	Yield (%)	Mp (°C)	Lit. mp (°C)
4	Et	82	77–78	79[a]
5	Me	78	77–79	82–83[a]
6	*n*-Pr	79	116–118	115–116[a]
7	Ph	90	127–129	130[a]
8	4-$CH_3OC_6H_4$	77	165	163–167[a]

[a] Bukingham, J. *Dictionary of Organic Compounds*, 5th ed.; Chapman & Hall: London. **4**, P-02429; **5**, A-00092; **6**, B-03494; **7**, B-00140; **8**, M-00529.

In a manner similar to the primary amides, treatment of *N*1,*N*3-diacylated 3,4-dihydropyrimidin-2(1*H*)-ones **2a**–**e** with 1 equiv of primary amines in THF at room temperature for 0.5 h furnished the corresponding secondary amides **9**–**23** in 60–96% yields (Scheme 1, Table 2). The products were purified by column chromatography and recrystallized from appropriate solvent. The primary amines used include arylamines (phenyl, 2-methoxyphenyl and 2-methylphenyl), alkylamines (butyl, *n*-butyl, *sec*-butyl and *n*-heptyl) or biogenic amines such as β-phenethyl, homoveratryl, tryptamine and methyl tryptophanate (racemic as well as enantiomers). Reactions of enantiomers of methyl tryptophanate furnished optically pure acylated products. The reactions of 2-phenylenediamine, however, required 2.0 equiv of the **2a** to furnish the diacylated product **17**. Similarly, reactions with 2-aminophenol and 2-aminothiophenol furnished products exclusively of N-acylation. The less basic and less nucleophilic OH and SH were not acylated under these conditions.

Table 2
Preparation (THF/rt) of secondary amides **9**–**23** (R^1CONHR^2) from R^2NH_2

Secondary amides	R^1	R^2	Yield (%)
9	Et	Ph	82
10	Et	2-$CH_3OC_6H_4$	90
11	Me	2-$CH_3C_6H_4$	65
12	Me	*n*-C_4H_9	80
13	Me	*sec*-C_4H_9	65
14	Me	*n*-C_7H_{15}	78
15	Et	2-HOC_6H_4	95
16	Et	2-SHC_6H_4	73
17	Et	2-$NHCOEtC_6H_4$	80
18	Et	$PhCH_2CH_2$	90
19	Et	3,4-Di-$MeOC_6H_3CH_2CH_2$	96
20	Et	3-(1*H*-Indolyl)CH_2CH_2	90
21	Et	DL-3-(1*H*-Indolyl)$CH_2CHCOOMe$	70
22	Et	D-3-(1*H*-Indolyl)$CH_2CHCOOMe$	62
23	Et	L-3-(1*H*-Indolyl)$CH_2CHCOOMe$	60

When *N*1,*N*3-diacylated 3,4-dihydropyrimidin-2(1*H*)-ones **2a**–**e** were reacted with secondary amines (diethyl, morpholine, piperidine, *N*-methyl homoveratryl and *N*-methyl aniline) in THF at room temperature for 0.5 h tertiary amides **24**–**28** (Scheme 1, Table 3) were obtained in 70–93% yields, after column chromatography of the crude residue.

Table 3
Preparation (THF/rt) of tertiary amides **24**–**28** ($R^1CONR^3R^4$) from R^3R^4NH

Tertiary amides	R^1	R^3	R^4	Yield (%)
24	Me	Et	Et	78
25	Me	$-(CH_2)_2-O-(CH_2)_2-$		74
26	Me	$-(CH_2)_5-$		80
27	*n*-Pr	3,4-Di-$MeOC_6H_3CH_2CH_2$	Me	93
28	*n*-Pr	Ph	Me	70

The fact that all these examples (Tables 1–3) including ammonia, primary aliphatic acyclic amines (*n*-butyl amine, *sec*-butyl amine and *n*-heptyl amine), secondary amine (diethyl amine) and heterocyclic counterparts: morpholine and piperidine, upon reaction with appropriate **2** conveniently furnish the corresponding acylated derivatives **4**–**28**, the steric factors do not affect the reaction in any significant way.

3. Conclusions

In summary, a simple and efficient method for the preparation of primary, secondary and tertiary amides has been developed by the treatment of readily available *N*1,*N*3-diacyl 3,4-dihydropyrimidin-2(1*H*)-one derivatives with ammonia, primary and secondary amines, respectively. The transformation is high yielding and runs under neutral conditions facilitating acylation of acid or base sensitive substituents. Work-up is easy and direct use of acid chlorides and anhydrides is avoided.

4. Experimental

4.1. General

All liquid reagents were dried/purified following recommended drying agents and/or distilled over 4 Å molecular sieves. THF was dried (Na-benzophenone ketyl) under nitrogen. ^{1}H NMR (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ on a multinuclear Jeol FT-AL-300 spectrometer with chemical shifts being reported in parts per million (δ) relative to internal tetramethylsilane (TMS, δ 0.0, ^{1}H NMR or $CDCl_3$, δ 77.0, ^{13}C NMR). Mass spectra

were recorded from Indian Institute of Integrative Medicine (CSIR), Jammu, under electron impact at 70 eV on a Bruker Daltonics Esquire 3000 spectrometer. Elemental analysis was performed on FLASH EA 112 (Thermoelectron Corporation) analyzer at Department of Chemistry, Guru Nanak Dev University, Amritsar and the results are quoted in %. IR recorded on FTIR Shimadzu 8400 Fourier-transform spectrophotometer in the range 400–4000 cm^{-1} using chloroform as medium. Melting points were determined in open capillaries and are uncorrected. For column chromatography silica gel (60–120 mesh) was employed and eluents were ethyl acetate/hexane mixtures.

4.2. Modified procedure for the preparation of (2)

To a stirred solution of DHPM **1**[5] (500 mg, 1.92 mmol) in dry THF (20 mL) at −20 °C, under a blanket of dry N_2, freshly prepared 2.0 N *n*-BuLi in hexanes (1.63 mL, 3.26 mmol) was introduced using syringe. The reaction was stirred at −20 °C for 0.5 h after which an appropriate acid anhydride (in the case of **2a**–**c**)/acid chloride (in the case of **2d**–**e**) (4.8 mmol) dissolved in dry THF (10 mL) was added to the reaction mixture at the same low temperature. After completion (TLC), the reaction was quenched with saturated aqueous solution of NH_4Cl (−78 ^{0}C) and the organic phase was washed with brine (10 mL) and extracted with ethyl acetate (3×30 mL). The extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The corresponding products **2a**–**e** were isolated using column chromatography.

*4.2.1. 5-Ethoxycarbonyl-6-methyl-1,3-dipropionyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**2a**).* Colourless solid; [Found: C, 64.78; H, 6.60; N, 7.30. $C_{20}H_{24}N_2O_5$ requires C, 64.51; H, 6.45; N, 7.52%]; R_f (35% EtOAc/hexane) 0.8; mp: 87 °C (DCM/hexane); ν_{max} ($CHCl_3$) 3060, 1710, 1220, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.19–7.29 (5H, m, ArH), 6.77 (1H, s, C4-H), 4.25 (2H, q, *J* 7.2 Hz, ester–CH_2), 3.07–3.10 (1H, m, $COCH_aH_bCH_3$), 2.74–2.83 (2H, m, $COCH_2CH_3$,), 2.52 (3H, s, C6–CH_3), 2.37–2.45 (1H, m, $COCH_aH_bCH_3$), 1.29 (3H, t, *J* 7.2 Hz, ester–CH_3), 1.23 (3H, t, *J* 7.2 Hz, CH_3CH_2CO), 0.95 (3H, t, *J* 7.2 Hz, CH_3CH_2CO); δ_C (75 MHz, $CDCl_3$) 175.6, 164.4, 155.6, 149.2, 137.4, 129.3, 128.7, 128.2, 126.4, 119.7, 61.3, 52.2, 31.7, 31.4, 19.6, 14.1, 9.0, 8.6; *m*/*z* 372 (M^+).

*4.2.2. 5-Ethoxycarbonyl-6-methyl-1,3-diacetyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**2b**).* Viscous liquid; [Found: C, 62.59; H, 5.92; N, 8.38. $C_{18}H_{20}N_2O_5$ requires C, 62.79; H, 5.81; N, 8.13%]; R_f (25% EtOAc/hexane) 0.9; ν_{max} ($CHCl_3$) 3015, 1650, 1600, 1220 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.19–7.31 (5H, m, ArH), 6.77 (1H, s, C4–H), 4.26 (2H, q, *J* 6.0 Hz, ester–CH_2), 2.59 (3H, s, C6–CH_3), 2.53 (3H, s, OCH_3), 2.26 (3H, s, OCH_3), 1.29 (3H, t, *J* 7.2 Hz, ester–CH_3); δ_C (75 MHz, $CDCl_3$) 171.5, 170.4, 164.2, 152.2, 149.3, 136.9, 128.7, 128.2, 126.1, 120.8, 61.3, 51.9, 26.0, 25.9, 19.9, 14.0; *m*/*z* 344 (M^+).

*4.2.3. 5-Ethoxycarbonyl-6-methyl-1,3-dibutyryl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**2c**).* Viscous liquid; [Found: C, 65.78; H, 6.90; N, 7.20. $C_{22}H_{28}N_2O_5$ requires C, 66.00; H, 7.00; N, 7.00%]; R_f (20% EtOAc/hexane) 0.7; ν_{max} ($CHCl_3$) 3150, 1700, 1640, 1220 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.18–7.28 (5H, m, ArH), 6.76 (1H, s, C4–H), 4.25 (2H, q, *J* 1.2 Hz, ester–CH_2), 3.04–3.12 (1H, m, $COCH_aCH_bCH_3$), 2.68–2.79 (2H, m, $COCH_2$), 2.52 (3H, s, C6–CH_3), 2.38–2.40 (1H, m, $COCH_aCH_bCH_3$), 1.67–1.75 (2H, m, CH_2CH_3), 1.43–1.47 (2H, m, CH_2CH_3), 1.29 (3H, t, *J* 7.2 Hz, ester–CH_3), 1.00 (3H, t, *J* 7.2 Hz, CH_3CH_2), 0.76 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 174.6, 173.7, 164.3, 152.0, 149.4, 137.4, 128.7, 128.1, 126.3, 119.9, 61.3, 52.0, 39.8, 39.7, 19.7, 18.2, 17.7, 14.1, 13.6, 13.3; *m*/*z* 400 (M^+).

*4.2.4. 5-Ethoxycarbonyl-6-methyl-1,3-dibenzoyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**2d**).* Viscous liquid; [Found: C, 71.59; H, 5.22; N, 5.68. $C_{28}H_{24}N_2O_5$ requires C, 71.79; H, 5.13; N, 5.98%]; R_f (30% EtOAc/hexane) 0.6; ν_{max} ($CHCl_3$) 3025, 1704, 1698, 1235, 758 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.12–7.57 (15H, m, ArH), 6.50 (1H, s, C4–H), 4.24 (2H, q, *J* 7.2 Hz, ester–CH_2), 2.44 (3H, s, C6–CH_3), 1.26 (3H, t, *J* 7.2 Hz, ester–CH_3); δ_C (75 MHz, $CDCl_3$) 170.9, 169.9, 165.0, 151.2, 146.4, 138.8, 134.7, 134.6, 133.6, 132.6, 131.9, 130.1, 128.8, 128.4, 128.2, 128.1, 126.8, 110.0, 61.2, 54.4, 16.8, 14.2; *m*/*z* 491 (M+23).

*4.2.5. 5-Ethyoxycarbonyl-6-methyl-1,3-bis(4-methoxybenzoyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**2e**).* Viscous liquid; [Found: C, 67.94; H, 5.10; N, 5.42. $C_{30}H_{28}N_2O_7$ requires C, 68.18; H, 5.30; N, 5.30%]; R_f (60% EtOAc/hexane) 0.3; ν_{max} ($CHCl_3$) 3020, 1710, 1650, 1370, 1220, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.30–7.65 (9H, m, ArH), 6.87–6.91 (2H, m, ArH), 6.65 (2H, d, *J* 9.0 Hz, ArH), 6.50 (1H, s, C4–CH_3), 4.31 (2H, q, *J* 7.2 Hz, ester–CH_2), 3.82 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 2.48 (3H, s, C6–CH_3), 1.30 (3H, t, *J* 7.5 Hz, ester–CH_3); δ_C (75 MHz, $CDCl_3$) 170.2, 168.7, 165.2, 164.9, 162.7, 151.4, 146.6, 139.3, 132.9, 130.6, 128.7, 128.0, 126.8, 125.1, 114.1, 113.5, 110.2, 61.0, 55.5, 55.3, 54.4, 16.6, 14.2; *m*/*z* 551 (M+23).

4.3. General procedure for the reaction of ammonia, primary and secondary amines with *N*1,*N*3-diacyl-3,4-dihydropyrimidin-2(1*H*)-one derivatives 2a–e

Appropriate *N*1,*N*3-diacyl-3,4-dihydropyrimidin-2(1*H*)-one derivative **2a**–**e** (1 mmol) dissolved in THF was added to stirred THF saturated with ammonia gas (evolved by warming 30% aqueous ammonia solution) and the reaction stirred for around 1 h at room temperature. After completion of the reaction (TLC), solvent was removed and the residue chromatographed to isolate pure products **4**–**8**. The isolated yields, melting points and reported melting points of the products are summarized in Table 1. Likewise, in the case of primary or secondary amines, appropriate amine (1.0 mmol) was added to a solution of appropriate **2a**–**e** (1.0 mmol) in THF and the corresponding products **9**–**23** (Table 2) and **24**–**28** (Table 3) isolated as described above.

*4.3.1. N-Phenylpropionamide (**9**)*[4]. Colourless solid; [Found: C, 72.20; H, 7.20; N, 9.10. $C_9H_{11}NO$ requires C, 72.48; H, 7.38; N, 9.39%]; R_f (30% EtOAc/hexane) 0.5; mp: 98–100 °C (DCM/hexane); ν_{max} ($CHCl_3$) 2990, 1655, 1600, 1440, 756 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.15 (1H, br s, exchanged with D_2O, NH), 7.07–7.52 (5H, m, ArH), 2.39 (2H, q, *J* 7.5 Hz, $COCH_2CH_3$), 1.25 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 172.0, 137.9, 128.9, 124.1, 119.7, 30.7, 9.6; *m*/*z* 172 (M+23).

*4.3.2. N-(2-Methoxyphenyl)propionamide (**10**).* Viscous liquid; [Found: C, 66.62; H, 7.43; N, 8.55. $C_{10}H_{13}NO_2$ requires C, 67.03; H, 7.26; N, 7.82%]; R_f (30% EtOAc/hexane) 0.6; ν_{max} ($CHCl_3$) 3030, 1650, 1610, 1220, 1120 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.32 (1H, dd, *J* 1.5, 1.8 Hz, ArH), 7.70 (1H, br s, exchanged with D_2O, NH), 6.78–6.98 (3H, m, ArH), 3.81 (3H, s, OCH_3), 2.36 (2H, q, *J* 7.5 Hz, $COCH_2CH_3$), 1.18 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 171.8, 147.5, 127.7, 123.3, 121.0, 119.6, 109.7, 55.6, 31.0, 9.6; *m*/*z* 202 (M+23).

*4.3.3. N-2-Tolylacetamide (**11**)*[3c]. Brownish solid; [Found: C, 72.40; H, 7.14; N, 9.62. $C_9H_{11}NO$ requires C, 72.48; H, 7.38; N, 9.39%]; R_f (40% EtOAc/hexane) 0.8; mp: 120–122 °C (DCM/hexane); ν_{max} ($CHCl_3$) 3010, 1680, 1220, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.74 (1H, d, *J* 7.8 Hz, ArH), 7.05–7.23 (3H, m, ArH), 6.99 (1H, br s, exchanged with D_2O, NH), 2.26 (3H, s, $COCH_3$), 2.20 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 168.0, 130.4, 129.4, 126.6, 125.3, 123.5, 24.2, 17.7; *m*/*z* 172 (M+23).

*4.3.4. N-Butylacetamide (**12**)*[7]. Viscous liquid; [Found: C, 62.32; H, 11.05; N, 12.10. $C_6H_{13}NO$ requires C, 62.60; H, 11.30; N, 12.17%]; R_f (40% EtOAc/hexane) 0.5; ν_{max} ($CHCl_3$) 2950, 1650, 1210, 760 cm^{-1};

δ_H (300 MHz, $CDCl_3$) 5.40 (1H, br s, exchanged with D_2O, NH), 3.24 (2H, q, *J* 7.2 Hz, CH_2NH), 1.97 (3H, s, $COCH_3$), 1.43–1.53 (2H, m, CH_2CH_2NH), 1.28–1.38 (2H, m, $CH_2CH_3(CH_2)_2$), 0.92 (3H, t, *J* 6.9 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 170.1, 39.3, 31.5, 23.1, 19.9, 13.6; *m*/*z* 116 (M+1).

*4.3.5. N-sec-Butylacetamide (**13**).* Viscous liquid; [Found: C, 62.35; H, 11.37; N, 12.24. $C_6H_{13}NO$ requires C, 62.60; H, 11.30; N, 12.17%]; R_f (30% EtOAc/hexane) 0.6; ν_{max} ($CHCl_3$) 2990, 1670, 1225 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.23 (1H, br s, exchanged with D_2O, NH), 3.85–3.95 (1H, m, CHNH), 1.98 (3H, s, $COCH_3$), 1.40–1.47 (2H, m, CH_2CH_3), 1.11 (3H, d, *J* 6.6 Hz, CH_3CH), 0.90 (3H, t, *J* 7.2 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 169.4, 46.6, 29.6, 23.4, 20.3, 10.2; *m*/*z* 138 (M+23).

*4.3.6. N-Heptylacetamide (**14**).* Viscous liquid; [Found: C, 68.66; H, 12.34; N, 9.17. $C_9H_{19}NO$ requires C, 68.78; H, 12.10; N, 8.91%]; R_f (35% EtOAc/hexane) 0.5; ν_{max} ($CHCl_3$) 2950, 1630, 1230 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.47 (1H, br s, exchanged with D_2O, NH), 3.23 (2H, q, *J* 7.2 Hz, CH_2NH), 1.97 (3H, s, $COCH_3$), 1.49–1.59 (2H, m, CH_2CH_2NH), 1.28–1.30 (8H, m, $(CH_2)_4$), 0.88 (3H, t, *J* 6.9 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 169.1, 39.6, 31.7, 29.5, 28.9, 26.8, 23.3, 22.5, 14.0; *m*/*z* 180 (M+23).

*4.3.7. N-(2-Hydroxyphenyl)-propionamide (**15**).* Brownish solid; [Found: C, 65.20; H, 6.30; N, 8.10. $C_9H_{11}NO_2$ requires C, 65.45; H, 6.66; N, 8.48%]; R_f (40% EtOAc/hexane) 0.7; mp: 62–64 °C (DCM/hexane); ν_{max} ($CHCl_3$) 3020, 1698, 1215, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.80 (1H, br s, exchanged with D_2O, OH), 7.45 (1H, br s, exchanged with D_2O, NH), 6.83–7.15 (5H, m, ArH), 2.50 (2H, q, *J* 7.5 Hz, $COCH_2CH_3$), 1.29 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 174.1, 148.6, 127.0, 122.0, 120.4, 119.7, 30.0, 9.8; *m*/*z* 165 (M^+).

*4.3.8. N-(2-Mercaptophenyl)propionamide (**16**)*[4]. Colourless solid; [Found: C, 59.30; H, 6.30; N, 7.52; S, 17.40. $C_9H_{11}NOS$ requires C, 59.66; H, 6.07; N, 7.73; S, 17.67%]; R_f (40% EtOAc/hexane) 0.5; mp: 105 °C (DCM/hexane); ν_{max} ($CHCl_3$) 3415, 3300, 1610 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.40 (1H, d, *J* 8.1 Hz, ArH), 7.98 (1H, br s, exchanged with D_2O, NH,), 6.97–7.43 (3H, m, ArH), 2.19 (2H, q, *J* 7.5 Hz, $COCH_2CH_3$), 1.14 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 174.0, 155.2, 139.9, 136.4, 132.1, 123.0, 120.8, 29.9, 9.4; *m*/*z* 180 (M−1).

*4.3.9. N-(2-Propionylaminophenyl)propionamide (**17**)*[4]. Colourless solid; [Found: C, 65.80; H, 7.50; N, 12.40. $C_{12}H_{16}N_2O_2$ requires C, 65.45; H, 7.27; N, 12.72%]; R_f (40% EtOAc/hexane) 0.3; mp: 115–118 °C (DCM/hexane); ν_{max} ($CHCl_3$) 3300, 1665, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.17 (2H, br s, exchanged with D_2O, NH), 7.06–7.36 (4H, m, ArH), 2.37 (4H, q, *J* 7.5 Hz, 2×$COCH_2CH_3$), 1.22 (6H, t, *J* 7.5 Hz, 2×CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 173.4, 137.0, 130.5, 126.0, 125.5, 30.1, 9.7; *m*/*z* 243 (M+23).

*4.3.10. N-Phenethylpropionamide (**18**).* Colourless solid; [Found: C, 74.30; H, 8.20; N, 7.50. $C_{11}H_{15}NO$ requires C, 74.57; H, 8.47; N, 7.90%]; R_f (40% EtOAc/hexane) 0.5; mp: 52–54 °C (DCM/hexane); ν_{max} ($CHCl_3$) 3020, 1700, 1655, 1215 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.17–7.34 (5H, m, ArH), 5.42 (1H, br s, exchanged with D_2O, NH), 3.52 (2H, q, *J* 6.9 Hz, CH_2NH), 2.81 (2H, t, *J* 6.9 Hz, CH_2Ph), 2.15 (2H, q, *J* 7.8 Hz, $COCH_2CH_3$), 1.12 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 173.0, 145.9, 128.7, 127.9, 126.5, 60.0, 55.8, 18.8, 14.1; *m*/*z* 178 (M+1).

*4.3.11. N-[2-(3,4-Dimethoxyphenyl)ethyl]propionamide (**19**).* Light brown solid; [Found: C, 65.90; H, 7.80; N, 5.50. $C_{13}H_{19}NO_3$ requires C, 65.82; H, 8.01; N, 5.90%]; R_f (50% EtOAc/hexane) 0.2; mp: 42–44 °C (DCM/hexane); ν_{max} ($CHCl_3$) 3020, 1700, 1210, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.70–6.81 (3H, m, ArH), 5.72 (1H, br s, exchanged with D_2O, NH), 3.85 (6H, s, 2×OCH_3), 3.47 (2H, q, *J* 6.9 Hz, CH_2NH), 2.75 (2H, t, *J* 6.9 Hz, CH_2Ph), 2.16 (2H, q, *J* 7.5 Hz, $COCH_2CH_3$), 1.13 (3H, t, *J* 3.6 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 173.7, 148.9, 147.0, 131.3, 120.5, 111.8, 111.3, 55.8, 40.5, 35.1, 29.6, 9.8; *m*/*z* 260 (M+23).

*4.3.12. N-[2-(1H-Indol-3-yl)ethyl]propionamide (**20**).* Viscous liquid; [Found: C, 72.13; H, 7.50; N, 12.62. $C_{13}H_{16}N_2O$ requires C, 72.22; H, 7.40; N, 12.96%]; R_f (40% EtOAc/hexane) 0.16; ν_{max} ($CHCl_3$) 3010, 1710, 1210, 740 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.20 (1H, br s, exchanged with D_2O, NH), 7.10–7.62 (4H, m, ArH), 7.03 (1H, s, 1H-indole), 5.53 (1H, br s, exchanged with D_2O, NH), 3.60 (2H, q, *J* 6.6 Hz, CH_2NH), 2.97 (2H, t, *J* 6.3 Hz, CH_2 indole), 2.11 (2H, q, *J* 7.5 Hz, $COCH_2CH_3$), 1.10 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 173.2, 122.0, 119.3, 118.6, 112.8, 111.2, 39.7, 29.7, 25.2, 9.7; *m*/*z* 217 (M+1).

*4.3.13. DL-3-(1H-Indol-3-yl)-2-propionylaminopropionic acid methyl ester (**21**).* Colourless solid; [Found: C, 65.41; H, 6.46; N, 10.52. $C_{15}H_{18}N_2O_3$ requires C, 65.69; H, 6.56; N, 10.21%]; R_f (40% EtOAc/hexane) 0.2; mp: 136 °C (DCM/hexane); ν_{max} ($CHCl_3$) 2900, 1700, 1210, 750 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.21 (1H, br s, exchanged with D_2O, NH), 6.98–7.54 (4H, m, ArH), 6.97 (1H, d, *J* 2.4 Hz, 1H-indole), 5.96 (1H, br s, exchanged with D_2O, NH,), 4.93–5.00 (1H, m, $CH(CH_2)NH$), 3.70 (3H, s, $COOCH_3$), 3.31–3.40 (2H, m, $CH_2CHCOOCH_3$), 2.18 (2H, q, *J* 7.8 Hz, $COCH_2CH_3$), 1.11 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 173.4, 172.5, 136.0, 127.7, 122.6, 122.1, 119.6, 118.5, 111.2, 110.0, 52.8, 52.3, 29.5, 27.5, 9.5; *m*/*z* 297 (M+23).

*4.3.14. D-3-(1H-Indol-3-yl)-2-propionylaminopropionic acid methyl ester (**22**).* Viscous liquid; [Found: C, 65.30; H, 6.20; N, 9.90. $C_{15}H_{18}N_2O_3$ requires C, 65.69; H, 6.56; N, 10.21%]; R_f (40% EtOAc/hexane) 0.2; $[\alpha]^{20}_D$ −4.00 (c 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 3440, 1700, 1215, 757 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.11 (1H, br s, exchanged with D_2O, NH), 7.07–7.52 (4H, m, ArH), 6.95 (1H, d, *J* 2.4 Hz, 1H-indole), 6.05 (1H, br s, exchanged with D_2O, NH), 4.92–4.98 (1H, m, $CH(CH_2)NH$), 3.68 (3H, s, $COOCH_3$), 3.30–3.39 (2H, m, $CH_2CHCOOCH_3$), 2.16 (2H, q, *J* 7.5 Hz, $COCH_2CH_3$), 1.09 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 173.4, 172.5, 136.0, 122.6, 122.1, 119.6, 118.5, 111.2, 110.0, 52.8, 52.3, 29.5, 27.5, 9.5; *m*/*z* 297 (M+23).

*4.3.15. L-3-(1H-Indol-3-yl)-2-propionylaminopropionic acid methyl ester (**23**).* Viscous liquid; [Found: C, 65.30; H, 6.30; N, 9.90. $C_{15}H_{18}N_2O_3$ requires C, 65.69; H, 6.56; N, 10.21%]; R_f (40% EtOAc/hexane) 0.2; $[\alpha]^{20}_D$ +4.00 (c 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 3320, 1710, 1210, 755 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.32 (1H, br s, exchanged with D_2O, NH), 7.00–7.45 (4H, m, ArH), 6.95 (1H, d, *J* 2.4 Hz, 1H-indole), 5.94 (1H, br s, exchanged with D_2O, NH), 4.85–4.91 (1H, m, $CH(CH_2)NH$), 3.61 (3H, s, $COOCH_3$), 3.23–3.28 (2H, m, $CH_2CHCOOCH_3$), 2.09 (2H, q, *J* 7.5 Hz, $COCH_2CH_3$), 0.99 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 173.4, 172.5, 136.0, 122.6, 122.1, 119.6, 118.5, 111.2, 110.0, 52.8, 52.3, 29.5, 27.5, 9.5; *m*/*z* 297 (M+23).

*4.3.16. N,N-Diethylacetamide (**24**)*[3h]. Viscous liquid; [Found: C, 62.30; H, 10.90; N, 11.97. $C_6H_{13}NO$ requires C, 62.60; H, 11.30; N, 12.17%]; R_f (30% EtOAc/hexane) 0.6; ν_{max} ($CHCl_3$) 3020, 1730, 1215 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.34 (4H, q, *J* 7.2 Hz, 2×CH_2CH_3), 2.09 (3H, s, $COCH_3$), 1.18 (6H, t, *J* 7.2 Hz, 2×CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 169.9, 42.86, 40.0, 21.2, 14.0, 13.0; *m*/*z* 138 (M+23).

*4.3.17. 1-Morpholin-4-yl-ethanone (**25**)*[3h]. Viscous liquid; [Found: C, 55.61; H, 8.40; N, 10.78. $C_6H_{11}NO_2$ requires C, 55.81; H, 8.53; N, 10.85%]; R_f (40% EtOAc/hexane) 0.5; ν_{max} ($CHCl_3$) 3350, 2750, 1700, 1655, 1240 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.61–3.70 (6H, m, 2×CH_2O and CH_2NCOCH_3), 3.46 (2H, t, *J* 4.8 Hz, CH_2NCOCH_3), 2.09 (3H, s, $COCH_3$); δ_C (75 MHz, $CDCl_3$) 169.1, 66.7, 66.5, 46.5, 41.7, 21.0; *m*/*z* 152 (M+23).

*4.3.18. 1-Piperidin-1-yl-ethanone (**26**)*[3h]. Viscous liquid; [Found: C, 66.01; H, 9.90; N, 10.80. $C_7H_{13}NO$ requires C, 66.14; H, 10.24; N,

11.02%]; R_f (40% EtOAc/hexane) 0.6; ν_{max} ($CHCl_3$) 3320, 1710, 1215 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.54 (2H, t, *J* 5.4 Hz, CH_2NCOCH_3), 3.38 (2H, t, *J* 5.4 Hz, CH_2NCOCH_3), 2.08 (3H, s, $COCH_3$), 1.53–1.56 (6H, m, $(CH_2)_3$); δ_C (75 MHz, $CDCl_3$) 168.7, 47.4, 42.4, 26.3, 25.4, 24.4, 21.4; *m*/*z* 150 (M+23).

*4.3.19. N-(3,4-Dimethoxyphenethyl)-N-methylbutyramide (**27**).* Viscous liquid; [Found: C, 67.70; H, 8.35; N, 5.01. $C_{15}H_{23}NO_3$ requires C, 67.92; H, 8.68; N, 5.28%]; R_f (60% EtOAc/hexane) 0.8; ν_{max} ($CHCl_3$) 2970, 1730, 1260, 757 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.64–6.82 (3H, m, ArH), 3.86 (6H, s, 2×OCH_3), 3.47–3.59 (2H, m, CH_2NCH_3), 2.89 (3H, s, NCH_3), 2.78 (2H, t, *J* 7.5 Hz, CH_2Ph), 2.05 (2H, t, *J* 7.8 Hz, $COCH_2CH_2$), 1.52–1.69 (2H, m, $CH_2(CH_2)CH_3$), 0.87 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 172.9, 148.9, 147.3, 131.0, 130.7, 120.6, 111.7, 55.7, 51.6, 49.8, 35.8, 34.4, 33.3, 18.3, 13.6; *m*/*z* 266 (M+1).

*4.3.20. N-methyl-N-phenylbutyramide (**28**).* Viscous liquid; [Found: C, 74.20; H, 8.10; N, 7.78. $C_{11}H_{15}NO$ requires C, 74.57; H, 8.47; N, 7.90%]; R_f (25% EtOAc/hexane) 0.7; ν_{max} ($CHCl_3$) 3320, 1760, 1215 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.16–7.44 (5H, m, ArH), 3.26 (3H, s, NCH_3), 2.04 (2H, t, *J* 6.6 Hz, $COCH_2CH_2$), 1.53–1.71 (2H, m, $CH_2(CH_2)CH_3$), 0.82 (3H, t, *J* 7.2 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 173.2, 144.2, 129.6, 128.9, 127.6, 127.3, 37.2, 35.9, 18.9, 13.8; *m*/*z* 178 (M+1).

4.4. Recycling of *N*3-acyl-3,4-dihydropyrimidin-2(1*H*)-one derivatives 3a–d

Typically, compound **3a** (500 mg, 1.58 mmol) was added to *n*-propionic anhydride (10 ml) and the solution refluxed overnight after which *n*-propionic anhydride was removed under reduced pressure and residue chromatographed to obtain diacyl derivative **2a** (388 mg, 66%). Likewise, compounds **3b–d** were recycled into the corresponding diacyl derivatives by treatment with corresponding anhydrides. Recycling of **3e** using *p*-methoxy benzoyl chloride did not furnish the corresponding diacyl derivative **2e**.

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References and notes

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, NY, 1999.
2. Vogel, A. I. *Text Book of Practical Organic Chemistry*; Addition Wesley Longman Limited: UK, 1997; pp 1363–1365.
3. (a) Sreedhar, B.; Arundhathi, R.; Reddy, M. A.; Parthasarathy, G. *Appl. Clay Sci.* **2009**, *43*, 425; (b) Guillard, S.; Aramini, A.; Cesta, M. C.; Colagioia, S.; Coniglio, S.; Genovese, F.; Nano, G.; Nuzzo, E.; Orlando, V.; Allegrette, M. *Tetrahedron* **2006**, *62*, 5608; (c) Prasad, H. S.; Srinivasa, G. R.; Gowda, D. C. *Synth. Commun.* **2005**, *35*, 1189; (d) Jang, J. H.; Kim, H. J.; Kim, J. N.; Kim, T. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 1027; (e) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226; (f) Yadav, V. K.; Babu, K. G. *J. Org. Chem.* **2004**, *69*, 577; (g) Petricci, E.; Mugnaini, C.; Radi, M.; Corelli, F.; Botta, M. *J. Org. Chem.* **2004**, *69*, 7880; (h) Nishiwaki, N.; Nishida, D.; Ohnishi, T.; Hidaka, F.; Shimizu, S.; Tamura, M.; Hori, K.; Tohda, Y.; Ariga, M. *J. Org. Chem.* **2003**, *68*, 8650; (i) Kondo, K.; Sekimoto, E.; Nakao, J.; Murakami, Y. *Tetrahedron* **2000**, *56*, 5843; (j) Katritzky, A. R.; He, H. Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210; (k) Ishii, Y.; Takeno, M.; Kawasaki, Y.; Muromachi, A.; Nishiyama, Y.; Sakaguchi, S. *J. Org. Chem.* **1996**, *61*, 3088; (l) Katoh, A.; Kondoh, S.; Ohkanda, J. *Heterocycl. Commun.* **1996**, *2*, 141; (m) Hegedus, L. S.; Perry, R. J. *J. Org. Chem.* **1985**, *50*, 4955.
4. Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B. K. *Eur. J. Org. Chem.* **2004**, 1254.
5. Kolosov, M. A.; Orlov, V. D.; Beloborodov, D. A.; Dotsenko, V. V. *Mol. Divers.* **2009**, *13*, 5.
6. Singh, K.; Singh, S. *Tetrahedron Lett.* **2006**, *47*, 8143.
7. Borah, R.; Deka, N.; Sarma, J. C. *J. Chem. Res., Synop.* **1997**, 110.